

## Appendix 2

## EXHIBIT 1

### Summary Evaluation of Zucapsaicin Confusability

#### Comparison to Known Error Pairs

According to a study published in 1999, the mean normalized edit distance for 1127 pairs of drug names known to be confusing was 0.45.<sup>1</sup> A matched set of non-confusing pairs had a mean normalized edit distance of 0.837. The normalized edit distance for *zucapsaicin/capsaicin* is 0.18. In other words, the *zucapsaicin/capsaicin* pair is considerably more similar than the average pair of names that have been reported in the literature as confusing. No other names in the Multum database had a normalized edit distance less than the mean (*zucapsaicin/capsin* = 0.45 and *zucapsaicin/duadacin* = 0.45).

#### Recall Memory

A recently published study of the relationship between similarity and pharmacists' errors in immediate free recall showed that errors actually *decreased* as similarity increased.<sup>2</sup> Basically, when asked to recall a list of three drug names, pharmacists could use a *rhyming heuristic* to search their memories for the to-be-remembered names. That is, if they knew a drug rhymed with *-aicin*, they could search their memories for all other *-aicin* names until they recognized the one they were trying to recall. Thus the practice of using common stems in USAN names (e.g., all antivirals end in *-avir*; all monoclonal antibodies end in *-mab*), increases pharmacists ability to remember all members of a given class of drugs. Based on their high similarity, one would expect pharmacists to associate *capsaicin* and *zucapsaicin* in their memories. This similarity would most likely also lead to inferences about similarity in pharmacologic category.

#### Recognition Memory

Recently published studies of pharmacists' recognition memory suggest that as similarity between drug names increases, the probability of recognition memory errors increases.<sup>3</sup> The measure used in that study was bigram-1b1a. The bigram-1b1a similarity between *zucapsaicin* and *capsaicin* is 0.82. This level of similarity was associated with significantly increased risk of recognition memory errors. One would conclude that a pair of names with this similarity would be more likely to be falsely recognized than a pair of names with a lower similarity score. In fact, increased rates of recognition memory errors began at a much lower level of similarity (i.e., at bigram-1b1a = 0.45).

#### Visual Perception

Recent studies of pharmacists visual perception of drug names suggest that: (a) more frequently prescribed names are more accurately identified than less frequently prescribed names; (b) the denser a name's *neighborhood*, the more difficult it is to perceive; and (c) the effects of neighborhood density are strongest when the names in the neighborhood are more frequently prescribed than the target name.<sup>4</sup> Since we did not have prescribing frequency information about *capsaicin*, and since *zucapsaicin* is yet to be marketed, our conclusions about visual perception are limited. We conclude simply that if *zucapsaicin* were approved, it would be a neighbor of *capsaicin*, and it would increase the density of *capsaicin*'s neighborhood, thereby making *capsaicin* more difficult to perceive and more prone to be confused.

### Overall Evaluation

Overall, I conclude that *zucapsaicin* is likely to be confused with *capsaicin*. This conclusion is based on several facts: (a) *capsaicin* and *zucapsaicin* have a similarity score in the >99<sup>th</sup> percentile of all pairs of USAN names; (b) they are substantially more similar than the average pair of names cited in the literature as being confusing; (c) they are similar in both spelling and pronunciation; (d) the similarity score for the pair is in the range where increased recognition memory errors would be expected; and (e) the two drugs share a common strength (0.075), common dosage form (cream) and common route of administration (topical). One factor mitigating against confusion is the fact that the products differ in their initial letters. Similarity in the initial part of words is a very important driving factor in confusion, and if two names have to differ by only two letters, it is best that those differences be at the beginning of the word.

### Limitations

This analysis is probabilistic. Most of the conclusions, therefore, must be interpreted in terms of relative likelihoods or probabilities. My research suggests very strongly that, for most types of confusion, the error rate increases as similarity increases. Thus, highly similar pairs of names are more likely to be confused than less similar pairs. The absolute rate of confusion, however, depends upon a wide variety of factors, some of which were not taken into account by this analysis. Among these are prescribing frequency, packaging, storage location, Rx vs. OTC status, the circumstances of use (home, emergency department, etc.), as well as the mood, experience, and fatigue of the user. In addition, although similarity is a known risk factor for confusion, it is not a perfect predictor. Cigarette smoking is a clear risk factor for lung cancer, but not all cigarette smokers get lung cancer (in fact, only about 10% do). Analogously, not all similar names will be confused, and low similarity does not guarantee against confusion. All one can say with confidence is that, on the whole, similarity tends to increase the risk of confusion. Thus, whenever possible, it is prudent to minimize similarity.

I did not study the brand names of these products. If their brand names differ, then this will reduce the probability of confusion in settings where drugs are identified by their brand names. If the brand names are similar, it will increase the probability of confusion.

Finally, I did not take into account the potential severity of a confusion error involving *capsaicin* and *zucapsaicin*. Such a judgment is outside my area of expertise, but I strongly recommend that you obtain an expert opinion on this matter, as it has important implications for regulators. Even a low probability of confusion may not be tolerated if the consequences are severe. In contrast, higher probabilities of confusion might be accepted if one were confident that little harm would result.

### References

1. Lambert BL, Lin S-J, Gandhi SK, Chang K-Y. Similarity as a risk factor in drug name confusion errors: The look-alike (orthographic) and sound-alike (phonological) model. *Med Care* 1999; 37:1214-1225.
2. Lambert BL, Chang K-Y, Lin S-J. Immediate free recall of drug names: effects of similarity and availability. *Am J Health-Syst Pharm* 2003; 60:156-168.
3. Lambert BL, Chang KY, Lin SJ. Effect of orthographic and phonological similarity on false recognition of drug names. *Soc Sci Med* 2001; 52:1843-1857.
4. Lambert BL, Chang K-Y, Gupta P. Effects of frequency and similarity neighborhoods on pharmacists' visual perception of drug names. *Soc Sci Med* in press.

# EDIT DISTANCE SEARCH

Fri Aug 29 11:01:00 CDT 2003

SEARCH ON ZUCAPSAICIN  
Spelling Search

No.	Rank	Drug Name	Edit Distance
1	1	CAPSAICIN	0.1818
2	29	CAPSIN	0.4545
3	33	DUADACIN	0.4545
4	45	EUCALYPTAMINT	0.5385
5	47	ACTACIN	0.5455
6	51	ACTICIN	0.5455
7	53	ANACIN	0.5455
8	83	ARICIN	0.5455
9	101	ASPIRIN	0.5455
10	470	BACITRACIN	0.5455
11	475	DURAGANIDIN	0.5455
12	477	DURASAL II	0.5455
13	481	FURACIN	0.5455
14	491	FURADANTIN	0.5455
15	495	IDARUBICIN	0.5455
16	498	JENAMICIN	0.5455
17	499	KUTAPRESSIN	0.5455
18	500	MIACALCIN	0.5455
19	502	MICRAININ	0.5455
20	504	MUTAMYCIN	0.5455
21	508	OCUTRICIN	0.5455
22	514	PAPACON	0.5455
23	517	PARAPLATIN	0.5455
24	523	RT CAPSIN	0.5455
25	524	STATICIN	0.5455
26	525	TRIAMINICIN	0.5455
27	531	TRIXAICIN	0.5455
28	533	TUSSAFIN	0.5455
29	535	TUSSCIDIN	0.5455
30	598	ICY HOT WITH CAPSAICIN	0.5909
31	599	AZO GANTRISIN	0.6154
32	549	SULFASALAZINE	0.6154
33	609	LITECOAT ASPIRIN	0.625
34	616	UNICAP WITH IRON	0.625
35	617	ACHROMYCIN	0.6364

36	618	ACTAMIN	0.6364
37	625	ADAPIN	0.6364
38	634	AK-TRACIN	0.6364
39	635	ALBAMYCIN	0.6364
40	636	AMIKIN	0.6364
41	642	AMLACTIN	0.6364
42	645	AMPHOCIN	0.6364
43	646	ANSAID	0.6364
44	664	APACET	0.6364
45	672	APPECON	0.6364
46	673	AQUAPHYLLIN	0.6364
47	674	ASACOL	0.6364
48	676	ASENDIN	0.6364
49	683	ASTELIN	0.6364
50	686	AURALGAN	0.6364

## EDIT DISTANCE SEARCH

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SEARCH ON ZUCAPSAICIN  
Phoneme Search

No.	Rank	Drug Name	Edit Distance
1	1	CAPSAICIN	0.1818
2	29	CAPSIN	0.4545
3	33	TRIXAICIN	0.4545
4	35	ICY HOT WITH CAPSAICIN	0.5
5	36	ACTICIN	0.5455
6	38	AK-TRACIN	0.5455
7	39	CALCIDRINE	0.5455
8	41	EC NAPROSYN	0.5455
9	53	JENAMICIN	0.5455
10	54	KANAMYCIN	0.5455
11	61	KUTAPRESSIN	0.5455
12	62	MASTUSSIN	0.5455
13	66	MOXILIN	0.5455
14	67	NAPROSYN	0.5455
15	123	OCU-TRACIN	0.5455
16	124	OCUTRICIN	0.5455
17	130	ROXICET	0.5455
18	144	STATICIN	0.5455
19	145	TRIAMINICIN	0.5455
20	151	ANALGESIC BALM WITH CAPSAICIN	0.5833
21	152	BANCAP HC	0.5833
22	156	SALONPAS PAIN PATCH WITH CAPSAICIN	0.6154
23	158	UNICAP CAPSULE	0.6154
24	160	UNICAP SENIOR	0.6154
25	162	ACHROMYCIN	0.6364
26	163	ACTACIN	0.6364
27	167	ADAPIN	0.6364
28	176	AKNE-MYCIN	0.6364
29	179	ALBAMYCIN	0.6364
30	180	AMOXICILLIN	0.6364
31	726	AMPHOCIN	0.6364
32	727	AMPICILLIN	0.6364
33	1024	AMTUSSIN	0.6364
34	1027	ANACIN	0.6364
35	1067	APACET	0.6364

36	1075	AQUAPHYLLIN	0.6364
37	1076	ARICIN	0.6364
38	1084	ASTELIN	0.6364
39	1087	BACITRACIN	0.6364
40	1092	BACTRAMYCIN	0.6364
41	1093	BETAPACE	0.6364
42	1101	BETAPACEAF	0.6364
43	1107	BIAXIN	0.6364
44	1163	CAF CIT	0.6364
45	1167	CAFFEDRINE	0.6364
46	1168	CALCET	0.6364
47	1170	CALCIONATE	0.6364
48	1171	CALCIQUID	0.6364
49	1173	CANDIN	0.6364
50	1175	CAP-PROFEN	0.6364